Future research should investigate the association between clinical outcomes and weight gain within recommended targets for various BMI groups. Standardisation of reporting of outcomes is required for meaningful interpretation of evidence, and clinical applicability of findings.

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I am the chief investigator of the National Institute for Health Research project HTA–12/01/50 (effects of weight management interventions on maternal and fetal outcomes in pregnancy: individual patient data [IPD] meta-analysis of randomised trials and model-based economic evaluation). The UPBEAT study contributes data to the IPD.

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Metformin and pregnancy outcomes in obese women

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Carolyn Chiswick and colleagues should be congratulated on their EMPOWaR study in *The Lancet Diabetes & Endocrinology* examining preventive medical intervention for improvement of fetal programming during pregnancy.[1] The objective of this randomised, double-blind, placebo-controlled, trial, was to establish whether metformin use led to improvements in maternal and fetal outcomes in obese pregnant women without diabetes, in particular in birthweight, which the investigators used as a surrogate marker for long-term adverse offspring outcome. Pregnant women with a BMI of 30 kg/m^2 or more and without diabetes received up to 2500 mg daily of metformin (n=223) or placebo (n=226) from 12 to 16 weeks' gestation until delivery. Mean birthweight at delivery did not differ between the metformin group (3462 g [SD 548]) and the placebo group (3463 g [660]). The primary outcome of *Z* score of birthweight percentiles for babies delivered liveborn at 24 or more weeks' gestation and standardised for sex, parity and gestation was similar between groups and the estimated effect size of metformin on the primary outcome was non-significant (adjusted mean difference of –0·029, 95% CI –0·217 to 0·158; p=0·7597). Furthermore, metformin had no effect on prevention of gestational diabetes or maternal weight gain compared with placebo.

This well-designed study is one of the first clinical trials to investigate preventive treatment in pregnant women in hopes of providing protection for the unborn child from long-term adverse effects later in life. The Barker hypothesis conceptualised the notion of fetal programming, claiming that the foundation for medical disorders encountered in childhood and adulthood are planted during fetal life.[2] For instance, infants that have been exposed to hostile pregnancy environments, such as maternal hypertension leading to fetal growth restriction, are susceptible to developing cardiovascular disease, overt diabetes, and hypertension themselves as adults.[3] Pregnant obese women inherently provide a similarly hostile pregnancy environment. These women are at risk of excessive gestational weight gain, development of gestational diabetes, and hypertension during pregnancy, including pre-eclampsia.[4] Importantly, findings from previous studies have shown higher birthweights in offspring of obese women, which have been associated with childhood obesity.[5,6] Thus, the vicious cycle of maternal obesity passing from generation to generation is perpetuated.

Pregnancy as an opportunity to intervene and break this viscous cycle is an appealing option for all health-care providers in perinatal medicine. The bold idea that


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what we do to the fetus during the short and finite period of pregnancy could change and even improve lifelong outcomes of offspring validates the whole concept of prenatal care. If this concept is true, this tiny window of opportunity should not be wasted. Pregnancy allows counseling for smoking cessation, vaccine administration, and screening for high-risk behaviours.

The idea that metformin administered during pregnancy could reduce birthweight in high-risk, obese pregnant women is not biologically implausible. Animal models, epidemiological studies, and systematic reviews suggest that newborn babies with high birthweights tend to develop obesity later in life.[5,6,7] Maternal insulin resistance and hyperglycaemia provides a mechanism for excessive neonatal birthweight. At this time, metformin, an insulin sensitiser, seems to be the best preventive treatment for obesity in pregnancy. However, Chiswick and colleagues reported no significant differences between mothers given metformin and those given placebo. Various reasons could explain these results. First, metformin was initiated late in the first trimester; perhaps it would have a greater effect if initiated in the peri-conceptual period. Common practice is to administer metformin before or near the onset of conception in women with polycystic ovary syndrome. A longer length of treatment, ranging from 8 to 12 weeks up to 2–3 years, decreases weight over time.[8] A second reason for an absence of difference in birthweight was the high rate of adverse effects on treatment adherence. Drug compliance was recorded in about two-thirds of patients. However, only 38% of patients in the metformin group complied with taking the highest dose of 2500 mg per day, and 62% complied with the 2000 mg per day regimen. The effects on weight change are noted at higher doses of metformin.[8] Thus, perhaps not enough patients took the medicine at sufficient doses to result in a significant difference in the primary outcome. Finally, the greatest difference in offspring weight as a result of maternal intervention might happen in childhood, rather than the newborn period, as shown in the MiG study.[9] Follow-up studies are planned for the EMPOWaR trial, and the MiG TOFU (The Offspring Follow-Up) study was done at 2 years of age to compare body composition in children of women who participated in the MiG trial.

Some data suggested a maternal benefit from metformin. Pregnant women who received metformin had a significant reduction in inflammatory markers C-reactive protein and interleukin 6. Additionally, fasting plasma glucose and insulin concentrations were lower at 28 weeks in women who received metformin than in those who received placebo, but these differences were not maintained at 36 weeks. Although changing glucose homeostasis throughout pregnancy might have played a part, poor study drug compliance late in gestation is more likely to have contributed to this finding. At this time, metformin should not be used to improve pregnancy outcomes in obese women. Although follow-up studies are planned in the offspring, future studies should also focus on potential maternal benefits from metformin, in both the short term and the long term.

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